REMARKS

Claims 1-14, 29, 34, 35, and 38-58 are pending and are the subject of the instant office action.

A "clean" version of the now pending claims 1-14, 29, 34, 35, and 38-58 is shown above. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attachment is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Each of the rejections and objections set forth in the office action is addressed below.

A. Claim Objections

The Examiner has objected to claim 40, and claims dependent thereon, as being of improper form. Applicants have amended the subject claims; namely, claim 40 has been amended to more clearly incorporate the language of claims 1 and 6 to clarify the language of the claim. The amendment is not intended to narrow the scope of the claims as originally presented.

It is believed that the amendment addresses the Examiner's objection, and withdrawal of the objection is accordingly requested.

B. Section 112 Rejections

Claims 1-4, 6-10, 13-14, 29, 34, 35, 40-41, 45-48, 58 and dependent claims 11-14, 38, 42-44, and 49-57 were rejected under Section 112, second paragraph, as being indefinite.

Claims 1-3 were rejected on grounds that it is not clear what range is intended by the language "at least about...%". Claims 1-3, and claims 49-50, have been amended to delete the term "about". This deletion of the term "about" is not intended to narrow the scope of any of the subject claims as originally presented, but rather to only clarify the language employed in the recited phrase. It is believed that the Examiner's concern is overcome by the amendment, and withdrawal of the rejection is requested.

Claim 1 was also rejected as being indefinite for reciting the term

"modulates" apoptosis. Applicants respectfully submit that the specification clearly teaches the skilled artisan that the RTD polypeptide blocks Apo-2 ligand induced apoptosis and functions as an inhibitory Apo-2L receptor (see, e.g., pages 8-9 and 63-65). Accordingly, it is believed that the claim is clearly understood by those skilled in the art. The claim has been amended, and withdrawal of the rejection is respectfully requested.

Claims 1, 6, and 41 were rejected as being indefinite on grounds that the term "native sequence" is unclear. Applicants believe the term is clearly and readily understood in view of the definition provided on page 12, lines 2-25. Nevertheless, in order to even clarify the claims further (without narrowing the intended scope of the claims) and advance the prosecution, the term has been deleted from claims 1, 4, 6 and 41. Claim 6 has likewise been amended to clarify the intended use of the term "fragment" in the claims. Withdrawal of the rejection is requested.

Claim 4 and 6-9 were rejected as being indefinite on grounds that the claims are drawn to sequences. The subject claims have been amended to correctly recite "polypeptides" or "nucleic acids". Withdrawal of the rejection is therefore requested. Claim 10 and claims dependent thereon were similarly rejected. These claims have likewise been amended, and it is believed these amendments also overcome the rejection.

Claims 13 and 14 were rejected on grounds that the term "immunoglobulin sequence" is unclear. Like the claims mentioned above, the term "sequence" has been deleted from the claims. As to the meaning of the term "immunoglobulin", it is respectfully submitted that the term will be readily understood to those skilled in the art in view of the specification. As taught on pages 40-45 of the specification, the chimeric molecules may comprise various forms, including immunoadhesins comprising immunoglobulin light or heavy chain constant regions. Withdrawal of this rejection is accordingly requested.

Claims 29 and 34 were rejected on grounds that it is unclear which polypeptide is referred to. It is respectfully believed that the claims do clearly recite the various forms of RTD polypeptide contemplated by the invention. Withdrawal of the rejection is requested.

Claims 34 and 35 were rejected as being indefinite on grounds that

it is unclear what the recited composition includes. The claims have been amended to recite that the composition includes a carrier and the RTD polypeptide. It is believed that the amendment addresses the instant rejection, and withdrawal of the rejection is thereby requested.

Claim 40 was rejected as being improperly drawn to a sequence. The claim, and its dependents, have been amended to delete the term 'sequence" and recite the term "polynucleotide" as suggested by the Examiner. It is believed that the amendment overcomes the rejection, and withdrawal of the rejection is requested.

Claims 45-47 were rejected on grounds that a cell cannot comprise a cell. The subject claims, along with claims 55-57, have been amended along the lines suggested by the Examiner, and withdrawal of the rejection is requested.

Claims 48 and 58 were rejected because of the claim format employed by Applicants. Claim 48 and 58 have been amended to recited methods of producing RTD polypeptides, as suggested by the Examiner, and accordingly, withdrawal of these rejections is also requested.

Claims 1-3, 6, 8, 9, 40, and 42-49 were rejected in the office action as being non-enabled. It is believed that the amendments to the subject claims address the Examiner's objections, and withdrawal of the Section 112, first paragraph, rejections is requested.

C. <u>Section 102 Rejection</u>

Claims 1-6, 8-14, 29, 38-45, 47-55, 57 and 58 were rejected under Section 102(e) as being anticipated by Ni et al., US Patent 6,124,580. Applicants respectfully traverse this rejection for the reasons below.

The Ni et al. patent claims priority from US Provisional application no. 60/050,936 filed May 30, 1997 (the "first priority application") and US Provisional application no. 60/069,112 filed December 9, 1997 (the "second priority application"). Accordingly, the first priority application of Ni et al. was filed before the August 26, 1997 priority filing date of the instant application. However, the second priority application of Ni et al. was filed after the August 26, 1997 priority filing date of the instant application. For the Examiner's convenience, Applicants are enclosing copies of the Ni et al. first and second

priority applications, along with a Supplemental Information Disclosure Statement and Form 1449 identifying these two applications.

The Ni et al. patent discloses a polypeptide, referred to as TR10, encoded by a cDNA cloned from a cDNA library. While the first priority application of Ni et al. discloses the cDNA sequence and deduced amino acid sequence of TR10, it fails to teach or suggest to one skilled in the art how to make and use the TR10 molecule. Example 4 in the Ni et al. first priority application (see pages 59-61 of first priority application) describes experimental results of certain Northern blot assays, but the data from those assays (e.g. that mRNA expression was found in multiple human normal and cancer cells and tissues) clearly does not provide sufficient disclosure as to the function of TR10. All of the remaining "examples" in the first priority application of Ni et al. are indeed prophetic, as can be seen from the fact that the examples are expressed throughout in the present tense.

The function, utility, and binding property(s) of the TR10 were solely postulated in the Ni et al. first priority application, based on sequence homology between the sequences of TR10 and other TNF receptor family members. The TR10 molecule was not actually expressed or tested by Ni et al., and therefore its function or utility was not experimentally determined. In particular, Applicants wish to point out at least two factors why Ni et al. were <u>not</u> in a position to postulate function or utility of TR10 at the time of filing their first priority application. First, Ni et al. themselves teach in their specification that the "effects of TNF family ligands and receptors are varied and influence numerous functions, both normal and abnormal, in the biological processes of the mammalian system." (First priority application at page 5, lines 6-8; see also, page 34, lines 4-25). Such teachings clearly indicate that Ni et al. could not have reasonably predicted what function or activity TR10 may or may not have. Second, it is important to note the prophetic Example 5 provided on pages 62-63 of the first priority application. Example 5 teaches that TR10 will exhibit apoptotic activity. This speculative teaching is clearly wrong, as taught by Applicants' instant application, and by Ni et al.'s later filed application (as noted below).

It is therefore submitted that the first priority application of Ni et al. is not enabling for TR10 and does not satisfy the requirements of Section 112 or Section 101.

The Ni et al. second priority application was filed December 9, 1997, which is after the August 26, 1997 priority filing date of the instant application. It was not until the second priority application that Ni et al. experimentally found that TR10 bound Apo-2 ligand or inhibited apoptotic activity by Apo-2 ligand. As noted above, this finding is completely opposite of that reported by Ni et al. in Example 5 of the first priority application.[1] Accordingly, the Ni et al. patent is not entitled to its May 30, 1997 priority filing date for purposes of Section 102(e) against the instant claims.

A careful analysis of the disclosures of the first and second priority applications of Ni et al. clearly reveals (1) that the first application only disclosed TR10 in a non-enabling manner and (2) that a description of how TR10 could be used was not disclosed at all until after the priority filing date of the instant application.

For all these reasons, the Ni et al. patent does not have effective 102(e) prior art status against the present application and does not anticipate the present claims. It is requested that the Section 102(e) rejection of the claims be withdrawn.

D. Section 103 Rejection

Claims 1-14, 29, 34, 35, and 38-58 were rejected under Section 103(a) as being unpatentable over Ni et al., US Patent 6,124,580. Applicants respectfully traverse the rejection.

As explained above, it is believed that Ni et al. is not properly entitled to its first application priority filing date, and therefore not

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[1]Compare the titles of Example 5 in the first priority application at page 62, "TR10 Induced Apoptosis", and that of Example 5 in the second priority application at page 41, "TR10 Inhibits TRAIL Induced Apoptosis."

properly cited as prior art against the present claims. Withdrawal of the rejection is respectfully requested.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Twice Amended) Isolated RTD polypeptide having at least [about] 80% amino acid sequence identity with [native sequence] RTD polypeptide comprising amino acid residues 1 to 386 of Fig. 1A (SEQ ID NO:1), wherein said isolated RTD polypeptide [modulates] inhibits Apo-2 ligand induced apoptosis in a mammalian cell or binds Apo-2 ligand.

2. (Once Amended) The RTD polypeptide of claim 1 wherein said RTD polypeptide has at least [about] 90% amino acid sequence identity.

3. (Once Amended) The RTD polypeptide of claim 2 wherein said RTD polypeptide has at least [about] 95% amino acid sequence identity.

4. (Once Amended) Isolated [native sequence] RTD polypeptide comprising amino acid residues 1 to 386 of Fig. 1A (SEQ ID NO:1).

6. (Twice Amended) Isolated extracellular domain [sequence of] RTD polypeptide comprising (a) amino acid residues 56 to 212 of Fig. 1A (SEQ ID NO:1); or (b) a fragment[s] of the sequence of (a) which [retain at least one biological activity of a native sequence RTD polypeptide] binds Apo-2 ligand or inhibits Apo-2 ligand induced apoptosis in a mammalian cell.

7. (Once Amended) The extracellular domain [sequence] polypeptide of claim 6 comprising amino acid residues 1 to 212 of Fig. 1A (SEQ ID NO:1).

8. (Once Amended) The [I]isolated extracellular domain [sequence of] RTD polypeptide of claim 6 comprising amino acid residues 99 to 139 of Fig. 1A (SEQ ID NO:1).

9. (Once Amended) The extracellular domain [sequence] polypeptide of claim 8 further comprising amino acid residues 141 to 180 of Fig. 1A (SEQ ID NO:1).

10. (Twice Amended) A chimeric molecule comprising the RTD polypeptide of claim 1 or claim 6 fused to a heterologous [amino acid sequence] polypeptide.

11. (Twice Amended) The chimeric molecule of claim 10 wherein said RTD polypeptide comprises an extracellular domain [sequence] of claim 6 comprising amino acid residues 56 to 212 of Fig. 1A (SEQ ID NO:1).

12. (Once Amended) The chimeric molecule of claim 10 wherein said heterologous [amino acid sequence] polypeptide is an epitope tag [sequence].

13. (Once Amended) The chimeric molecule of claim 10 wherein said heterologous [amino acid sequence] polypeptide is an immunoglobulin [sequence].

14. (Once Amended) The chimeric molecule of claim 13 wherein said immunoglobulin [sequence] is an IgG.

34. (Twice Amended) An article of manufacture, comprising a container and a composition contained within said container, wherein the composition includes a carrier and the RTD polypeptide of claim 1 or claim 6.

40. (Once Amended) Isolated nucleic acid comprising a polynucleotide [sequence] encoding [the RTD polypeptide of claim 1 or the extracellular domain sequence of claim 6] a polypeptide selected from the group consisting of:
a) a polypeptide comprising amino acid residues 1 to 386 of Fig. 1A (SEQ ID NO:1);
b) a polypeptide comprising amino acid residues 56 to 212 of Fig. 1A (SEQ ID NO:1); and
c) a fragment of the polypeptide of (a) or (b) which binds Apo-2 ligand.

41. (Once Amended) The nucleic acid of claim 40 wherein said polynucleotide [sequence] encodes [native sequence] RTD polypeptide comprising amino acid residues 1 to 386 of Fig. 1A (SEQ ID NO:1).

45. (Once Amended) The host cell of claim 44 which [comprises] is a CHO cell.

46. (Once Amended) The host cell of claim 44 which [comprises] is a yeast cell.

47. (Once Amended) The host cell of claim 44 which [comprises] is *E. coli*.

48. (Once Amended) A process of [using a nucleic acid molecule encoding] producing RTD polypeptide [to effect production of RTD polypeptide] comprising culturing the host cell of claim 44, wherein said nucleic acid comprised by said vector is expressed to produce the RTD polypeptide of claim 1 or claim 6.

49. (Once Amended) The nucleic acid of claim 40 wherein said encoded RTD polypeptide has at least [about] 90% amino acid sequence identity with the RTD polypeptide comprising amino acid residues 1 to 386 of Fig. 1A (SEQ ID NO:1).

50. (Once Amended) The nucleic acid of claim 49 wherein said encoded RTD polypeptide has at least [about] 95% amino acid sequence identity with the RTD polypeptide comprising amino acid residues 1 to 386 of Fig. 1A (SEQ ID NO:1).

51. (Once Amended) The nucleic acid of claim 40 wherein said polynucleotide [sequence] comprises the nucleotide coding region shown in SEQ ID NO:2.

55. (Once Amended) The host cell of claim 54 which [comprises] is a CHO cell.

56. (Once Amended) The host cell of claim 54 which [comprises] is a yeast cell.

57. (Once Amended) The host cell of claim 54 which [comprises] is *E. coli*.

58. (Once Amended) A process of [using a nucleic acid molecule encoding] producing RTD polypeptide [to effect production of RTD polypeptide] comprising culturing the host cell of claim 54, wherein said nucleic acid comprised by said vector is expressed to produce the RTD polypeptide of claim 40.